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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,894	07/07/2003	James M. Hagberg	108172-00097	7034

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,894	HAGBERG ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *21-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending.
Claims 21-27 are withdrawn.
Claims 1-20 are examined on the merits

This Office Action is in reply to Applicants' correspondence of 08/25/2006. No claims are cancelled; claims 21-27 are withdrawn; claims 19-27 have been newly added; claims 1 and 7-18 have been amended. Applicants' remarks and amendments have been fully considered but are not found to be persuasive.

Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn.

This Action is made FINAL.

Withdrawal of newly presented claims

1. Newly submitted claims 21-27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The originally presented claims were directed to methods requiring only the identification of the PAI-1 alleles of an individual. The newly presented claims require only the identification of the t-PA alleles of an individual; if the newly presented claims were originally presented they would have been subjected to a Requirement for Restriction. In the instant case, claims drawn to the analysis of genotypes of different genes are patentably distinct because they require the analysis of unique nucleic acid sequences that are in fact not common to one another. One would not expect a reference regarding phenotypes associated with particular PAI-1 alleles to also be a reference regarding the same phenotype associated with t-PA alleles.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, claims 21-27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

The following rejection is a NEW REJECTION necessitated by Applicant's amendment to the claims.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 are unclear over recitation of the parenthetical term '(t-PA)' in claims 1, 7, and 13. It is not clear if applicant intends to claim an I allele of a particular gene locus as it is not clear if the parenthetical term is a specified limitation of a gene locus,

or a non-limiting example of where one might find an 'I allele'. Additionally, the term t-PA, not accompanied by a more detailed indication of a gene, is unclear. The claims may be made more clear if '(t-PA)' is edited to read 'tissue plasminogen activator (t-PA)', if that is in fact what applicant intends.

Claim Rejections - 35 USC § 112 1st¶ - New Matter

The following rejection is a NEW REJECTION necessitated by Applicant's amendment to the claims.

5. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

6. The claims of the instant application are drawn to a method of increasing fibrinolysis in a subject comprising the identification of subjects with particular PAI-1 alleles **and** particular alleles at the t-PA gene locus. However, the instant specification does not provided a basis for the identification of individuals with specific PAI alleles and specific t-PA alleles in a method of increasing fibrinolysis by engaging the subject in exercise.

The specification indicates that the invention is directed to a method comprising 'identifying a subject having an allele and/or genotype at **a** particular gene locus' (emphasis added, which indicates the analysis of alleles in a single gene) (specification ¶[0006]). The specification further indicates that the 'inventors have investigated the

plasminogen activator inhibitor-I (PAI-1) gene promoter site, in particular genotypes 4G/5G, 4G/4G, and 5G/5G' (specification ¶[0011]).

While the specification provides some data regarding the association of I and D t-PA genotypes with t-PA activity and antigen levels in response to exercise, the specification does not specifically contemplate the use of PAI genotype **in combination with** t-PA genotype in an individual as indicative of increased fibrinolysis in response to exercise.

Claim Rejections - 35 USC § 112

This rejection contains new grounds of rejection as necessitated by Applicants' amendments to the claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide a method to increase fibrinolysis, prevent cardiovascular disease, or ameliorate cardiovascular disease in a subject, for which the PAI-1 gene promoter and t-PA gene locus genotype has been determined, using exercise.

Nature of the Invention and Breadth of the Claims

The specification asserts that the instant invention relates to identifying genetic markers that correlate with improved success in increasing fibrinolysis levels in subjects through exercise training (paragraph [0003]). The claims are drawn to methods for effecting change in subjects with particular genotypes at the PAI-1 gene promoter polymorphic site using exercise training. Claims 1-6, 18 and 20 are drawn to methods for increasing fibrinolysis in a subject. Claims 7-12 are drawn to methods for preventing cardiovascular disease in a subject. Claims 13-18 are drawn to methods for ameliorating cardiovascular disease in a subject.

The claims encompass subjects with at least one 4G allele (i.e. both homozygous 4G/4G subjects and heterozygous 4G/5G subjects) (claims 1, 4-7, 10-13, 16-20), subjects with heterozygous (i.e. 4G/5G) genotypes (claims 2, 8, and 14), and subjects with homozygous 4G/4G genotypes (claims 3, 9, and 15). The claims encompass exercise regimens comprised of extensive exercise (claims 4, 10, and 16), moderate exercise (claims 5, 11, and 17), and limited exercise (claims 6, 12, and 18). Claim 19 requires that the subject is homozygous for the t-PA I allele, and claim 20 requires that the subject is heterozygous (I/D) for the t-PA allele.

The claims encompass any subject organism that contains the PAI-1 gene.

The nature of the invention requires knowledge of a correlation between the specific PAI-1 gene promoter and t-PA genotypes of a subject and the response (with regard to fibrinolysis levels) of that subject to exercise training.

Direction provided by the specification and working example

The specification teaches an example in which subjects were analyzed for several parameters indicative of fibrinolysis levels (i.e. PAI-1 and t-PA activities and t-PA antigen (paragraph [0031]) prior to participation in an exercise program to establish baseline values, and then after participation in an exercise program (paragraph [0045]).

The specification further teaches the genotyping of the PAI-1 gene promoter with respect to the 4G/5G polymorphic site (paragraph [0042]) by PCR amplification followed by restriction enzyme analysis of the resulting amplicon.

The instant specification provides an analysis of the changes in the measured parameters among the three possible (4G/4G; 4G/5G; 5G/5G) PAI-1 genotypes. The data indicate the following results: the average PAI-1 activity decreased for the 4G/4G and 5G/5G groups, and increased for the 4G/5G group; the average t-PA activity increased for all groups; the average t-PA antigen decreased for all groups. While the specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The specification further teaches an analysis of the changes in t-PA activity and t-PA antigen among the three t-PA genoptypes (I/I; I/D; D/D). The data indicate the following results: the average PAI-1 activity increased for the I/I and I/D groups, and decrease for the D/D group; the average t-PA antigen decreased for the I/I and I/D

groups, and increased for the D/D group. The analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The instant specification does not provide any data concerning any sort of control group, for example a reference group that did not participate in an exercise program.

The specification asserts that improving fibrinolysis prevented the development of cardiovascular disease or alleviated symptoms of cardiovascular disease (paragraph [0007]). There is no indication that either of these two qualities was actually measured in any of the analyzed subjects; Example 1 indicates that subjects were in fact excluded from the study if they had cardiovascular disease.

The specification does not provide any examples in which the genotype of a subject was identified at both the PAI-1 promoter and the t-PA gene locus.

The specification presents results only from a population of human male and female subjects age 50-70.

The specification presents results only from participation in moderate exercise training (paragraph [0047], Table 1). The specification provides no results from subjects that participated in extensive exercise, or subjects that were involved only in limited exercise.

State of the art, level of skill in the art, and level of unpredictability

The level of skill in the art with regard to identification of PAI-1 gene promoter and t-PA genotypes is high, however the prior art and the instant specification shows that the level of unpredictability in correlating any particular individual's genotype with fibrinolysis levels in response to exercise is high.

Väisänen et al teaches an analysis of fibrinolytic activity response to exercise among groups of subjects with different PAI-1 gene promoter genotypes. Although the Väisänen reference was applied to the art rejection earlier in this Office Action, the reference is cited in this enablement rejection to demonstrate the state of the art and its unpredictability; the specification of the instant application cannot be considered enabling for the methods of Väisänen because the instant application does not present the same data, gathered from the same population, as Väisänen. The Väisänen reference indicates that PAI-1 activity decreases (thus an indicator of increased fibrinolysis) in subjects from all subject groups regardless of PAI-1 genotype, as well as in reference groups (who do not participates in exercise) with both the 4G/4G and 4G/5G genotypes (Table 1). While the reference indicates that only the decrease in PAI-1 activity seen in the 4G/4G exercise group is significant (p=0.025; Table 1), the reference also indicates that the findings need to be replicated in other controlled randomized exercise studies (p.1119, right col., lns.52-53).

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis is illustrated by the instant specification. Table 1 (paragraph [0047]) indicates p-values from ANOVA analysis of several fibrinolysis related parameters that range from 0.189 to 0.802. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that

values above the conventional reference point of p=0.05 would not be considered strong enough for the basis of a conclusion.

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis is further exemplified by Tiyasangthong (2001). Tiyasangthong examine the hypothesis that exercise training effects fibrinolytic variables (p.103), and that the changes in PAI-1 activity with exercise training is related to PAI-1 polymorphisms (p.107). The reference indicates that there is no statistically significant correlation in changes in the measures of fibrinolytic parameters (PAI-1 and t-PA activity, and t-PA antigen) with regard to PAI-1 gene promoter genotype (p.95; p.96, Table 7).

With regard to the analysis of the t-PA I/D allele, the unpredictability of using this allele as a predictor of fibrinolysis in response to exercise training is demonstrated by the data of the instant specification. For example, the data of Table 2 indicates that there is no significant association between fibrinolysis in response to exercise (as measured by t-PA activity or t-PA antigen) and t-PA genotype of an individual. The specification indicates that t-PA antigen is decreased in subjects with t-PA genotypes I/I and I/D, which given the definition of 't-PA antigen' provided in the specification where 't-PA antigen' is 'the t-PA composition that stimulates fibrinolysis' (specification ¶[0013]), would seem to indicate that decreased t-PA antigen is indicative of decrease t-PA activity and thus decreased fibrinolysis. However, a measure of t-PA antigen is in fact not a measure of fibrinolysis, merely a measure of the amount of t-PA antigen present in a blood sample, whereas actual t-PA activity is required for fibrinolysis. Additionally,

although t-PA antigen is not a measure of fibrinolysis, the data of table 2 indicates that the P ANOVA of t-PA genotype associated with t-PA antigen is 0.054 which is not statistically significant. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion.

Furthermore, claims drawn to methods for preventing cardiovascular disease may be considered as encompassing those methods which completely keep even the most minor forms of cardiovascular disease from occurring; wherein the pertinent method step is engaging a subject in exercise training. And while there may be an inverse relationship between physical activity and the risk of developing cardiovascular disease, the prior art of Sesso et al (2000) indicates that participation in physical exercise is not sufficient to provide a guaranteed prevention of any form or type of cardiovascular disease (Table 2; p.976, right col., lns.44-53).

Quantity of experimentation required

There would be a large amount of experimentation required to make and use the claimed invention. In order to establish that there is any statistically significant association between PAI-1 gene promoter and t-PA gene genotype and response to exercise, one would have to conduct a large case-control randomized study to compare fibrinolytic activity among subjects with different PAI-1 and t-PA gene genotypes upon

exposure to exercise training. Such a study may or may not indicate that there is a reliable and statistically significant exercise dependent increase in fibrinolytic activity, prevention of cardiovascular disease, or amelioration of cardiovascular disease, that is associated with a subject's PAI-1 and t-PA genotype in any particular population.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention.

Response to Remarks

Applicant has traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement. Applicants' arguments and amendments to the claims have been fully and carefully considered but are not found to be persuasive.

Applicants argue (p.10-11 of Remarks) that the specification teaches various tendencies in the response to exercise of subjects with the 4G/4G PAI-1 genotype or subjects with the at least on I allele of the t-PA gene. This argument is not found to be persuasive for the reasons set forth in the rejection (i.e.: none of the P-values presented in specification are less than the 0.05 value required for statistical significance; there is in fact no example of identifying both the PAI-1 genotype and the t-PA genotype of any individual, and measure of t-PA activity is not a measure of fibrinolysis).

Applicant argues that improving the levels of fibrinolysis prevents the development of or alleviates the symptoms of cardiovascular disease (p.11 of Remarks). This is not found to be persuasive because applicant has not in fact shown that the increased level of fibrinolysis alleged by the data of the instant specification is in fact physiologically relevant to the removal of fibrin clots, or that any such cardiovascular benefits are associated with the PAI-1 and t-PA genotypes of a subject individual in any statistically significant way.

Applicants note that a reference or control is available in that the base line of the subjects was measured prior to exercise (p. 11 of Remarks). This is not found to be persuasive as the specification indicates that factors such as diet and environment may contribute to an individual's level of fibrinolysis as a result of exercise (specification ¶[0005]). Thus merely determining a baseline of a study subject prior participation in the study would not be expected to be an adequate control for factors such as environmental factors which may effect measures of fibrinolysis regardless exercise participation.

Applicants argue that the data reported in the Tiyansangthong dissertation was expanded to a larger study as reported in Table 1 of the instant specification, and the dissertation does not demonstrate the unpredictability of associating PAI-1 genotype with fibrinolysis. For the reasons set forth in the rejection, the examiner maintains that none of the data presented in the instant specification indicates a statistically significant association ($p<0.05$) between PAI-1 and t-PA genotypes and exercise-induced increase fibrinolysis. Thus the data of the instant specification do not teach a reliable method for

increasing fibrinolysis of a subject by identifying the PAI-1 and t-PA genotype of the subject and engaging the subject in exercise.

The rejection is MAINTAINED.

Response to Requirement For Information

Applicant has responded to the Requirement For Information Under 37 C.F.R. 1.105. Applicant indicates that the Tiyasangthong dissertation was made publicly available on Jan 22, 2003.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER